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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,896	08/25/2000	Jeffrey L. Cleland	P0998D2	6985

7590 12/19/2001

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1642	6

DATE MAILED: 12/19/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,896	CLELAND ET AL.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08-25-2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26,28-34,37-50* is/are pending in the application.

4a) Of the above claim(s) *1-25,27,35 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,28-34,37-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The examiner of the application has been changed. This case has now been transferred as of 20 November 2001. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.

2. Applicant's amendment is herewith acknowledged. Accordingly, Claims 1-25, 27, 35-36 have been canceled without prejudice. Claims 26, 28-34, 37-50 are pending and are being examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26, 28-34, 37-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Although the specification provides sufficient evidence for the production and construction of the lyophilized formulation of anti-HER2 and IgE antibodies, it does not provide clear direction as to how the formulation can be used for the treatment of cancer.

Claims 26, 28-34, 37-41 are drawn to a method of treating endometrial, lung, colon, bladder cancers, and ductal carcinoma *in situ* using a lyophilized anti-HER2 antibody, that can be reconstituted to a concentration of 10-30 mg/ml with a stability of 30 days at 2-8°C. The specification discloses the methodology of making the formulation from manufacturing to testing the stability of the lyophilized antibody, but the specification does not disclose how to use the claimed invention to treat cancer of the types described above. There is no evidence that the claimed invention is capable of working either in an *in vitro* or in an *in vivo* situation. There are no working examples that would provide one of skill in the art with the evidence that the claimed lyophilized antibody is capable of working effectively either in an *in vitro* situation for the elimination of cells expressing HER2 or in an *in vivo* situation for the treatment of a malignant phenotype. One of skill in the art would be forced into undue experimentation to practice the claimed invention because the specification does not provide a teaching as to the properties of the anti-HER2 lyophilized antibody for the treatment of the cancers described in the claims. Although it is well known in the art that anti-HER2 antibodies are used for the treatment of certain types of cancer, such as breast cancer (Sikic BI. Ann Oncol 1999;10 Suppl 6:149-53), the formulation for the anti-HER2 antibody as disclosed in the claims or specification may not function in the same manner as other efficacious anti-HER2 antibodies already in the prior art. The said formulation, because of the addition of other additives such as lyoprotectants and bulking agents, may render the product ineffective, by masking the ability of the antibody to function or by changing the antibody specificity or the ability of the claimed antibody to bind to the antigen with

the same affinity or binding parameters. There is no evidence in the specification that would allow one of skill in the art to use the said claimed formulation to treat cancer with a reasonable amount of success. No guidance is provided for all of these points as set forth above.

In case the applicant is able to successfully overcome these 35 USC§112, first paragraph rejections, the same claims can be rejected under 35 USC § 103.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

Claims 26, 28-34, 37-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valone FH *et al.* (J Hematother 1995; 4(5):471-5 see abstract) in view of Press MF *et al.* (Oncogene 1990;5(7):953-62) and Natali PG *et al* (Int J cancer

1990 Mar 15; 45(3):457-61) and further in view of Burton SC et al. (Am J Vet Res, 1981 Feb, 42(2):308-10, see abstract).

Claims 26, 28-34, 37-41 are directed to a method of treating patients suffering from endometrial, lung, colon, bladder and ductal carcinoma *in situ* cancers disclosed in the claims with a formulation consisting of a lyophilized ant-HER2 antibody, bulking agents, lyoprotectant, buffer and surfactants.

Valone *et al* teaches the treatment of patients suffering from advanced breast or ovarian cancer using a bispecific antibody to FcRI receptors and HER2, here termed MDX-210.

Press *et al* teaches the examination of HER2 expression in normal fetal and adult human tissues. This teaching describes expression of HER2 in epithelial cell membranes in the gastro-intestinal tract (large intestine), respiratory tract (bronchi), reproductive tract (uterus-endometrium), urinary tract (bladder), skin (epidermis), breast and placenta. In addition, it also teaches the potential to use this antigen, HER-2/*neu* as a diagnostic and therapeutic agent by examining alterations in expression levels of this protein in human tumors.

Natali PG *et al.* teaches the expression of HER2 in normal and transformed human tissues. This teaching describes the immunohistochemical examination of normal tissue and various tumors with monoclonal anti-HER2 antibodies, with positive staining results in breast, ovary and colon. In addition it also teaches the use of HER2 as a tumor marker.

Valone *et al.*, Press *et al.,* and Natali *et al.* all teach of HER2 and the use of it as an agent for cancer therapies, however, they all differ from the instant invention by not teaching the use of a lyophilized formulation of anti-HER2 antibody.

Burton *et al.* teaches the use of a lyophilized serum as a source of antibodies for neonatal foals. This teaching describes the methodology and use of a lyophilized serum for the immunization of newborn foals.

Therefore, it would have been *prima facie* obvious for one of ordinary skill in the art to combine the teachings of Valone *et al.,* Press *et al.,* Natali PG *et al.,* and Burton *et al.* to derive a treatment of cancers using an antibody directed against HER2 that was lyophilized, and one would have been motivated to combine the references because the use of an anti-HER2 antibody for the treatment of cancer was well known in the art as an efficacious treatment of ovarian and breast cancer types. It was also well known at the time the invention was made that HER2 is found on various cell types, tumors, and is a marker for diagnosis of HER2 associated cacners as described in Press *et al.*, and Natali *et al.* therefore one of ordinary skill in the art would expect that a reasonable amount of success would have been achieved if one combined the teachings to treat cancer using an anti-HER2 antibody for endometrial, lung, colon, bladder, and ductal carcinoma *in* situ. In addition, it would have been obvious to one of ordinary skill in the art to have also combined the teaching set forth above with those of Burton *et al* to make an antibody that was in a lyophilized form to administer to cancer patients.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

GEETHA P BANSAL
PRIMARY EXAMINER

Christopher Yaen
Patent Examiner, Art Unit 1642
December 14, 2001